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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,813	04/13/2007	Ulrich Bogdahn	JCLA21512	6647

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4 VENTURE, SUITE 250
IRVINE, CA 92618

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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03/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,813	BOGDAHN ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *March 1, 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed November 12, 2009.

Claim 19 has been amended.

Claims 19-21, and 23 are pending in the instant application.

Claims 19-21, and 23 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed March 1, 2010 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Nucleotide Sequence Disclosures

In the previous Office Action mailed August 11, 2009, it was noted that the instant application failed to comply with the requirements of 37 C.F.R. §1.821-1.825 because a Sequence Listing in both computer readable form (CRF) and paper copy could not be located in the file.

Response to Arguments

In response to this notice, Applicants have provided new Sequence Listing in both computer readable form (CRF) and paper copy in the reply filed on November 12, 2009. It is noted that this reply puts the application in compliance with the sequence requirements of 37 C.F.R. §1.821-1.825.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed August 11, 2009, claims 19-21, and 23 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising the direct or local administration of a therapeutically effect amount of SEQ ID NO:3, does not reasonably provide enablement for a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising administering a therapeutically effective amount of least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO:1, comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding TGF-R_{II} or a region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed August 11, 2009.

Response to Arguments

In response to this rejection, Applicants arguement is three-fold. First, Applicants argue that claim 19 has been amended to delete the term, "termination codon". Applicants contend that:

> "Claim 19 refers now to oligonucleotides that are directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} only. This is the same region the oligonucleotide with SEQ ID NO:3 is directed to".

This argument has been fully considered by the Examiner but is not found persuasive because contrary to Applicant's assertions, claim 19 does not now refer to oligonucleotides that are directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} only. Instead, claim 19 refers to oligonucleotides that are directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} or oligonucleotides that are directed to the region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure.

Furthermore, Applicants contend that oligonucleotides that are directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} are the same as SEQ ID NO:3. However, this too is not found persuasive because it doesn't appear that SEQ ID NO:3 is directed to a region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II}. Instead, SEQ ID NO:3 is complementary to nucleotides 86729-86744 of SEQ ID NO:1, where SEQ ID NO:1 is the ORF of the gene encoding TGF-R_{II}.

Applicant is reminded that the disclosure of the instant application has disclosed only one TGF-βRII antisense oligonucleotide that functions in a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal as claimed. See SEQ ID NO:3. However, it is does not appear that SEQ ID NO:3 is directed to an oligonucleotide that is directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} or an oligonucleotide that is directed to the region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure as claimed in claim 19.

Applicants secondly argue that Examples 6-8 of the specification prove that SEQ ID NO:3 has activity in promoting successful regeneration and functional reconnection of damaged neural pathways. Applicants aruge that because the oligonucletides claimed by amended claim 19 contain SEQ ID NO:3 and have a sequence very similar to SEQ ID NO:3, the oligonucletides claimed by amended claim 19 should show the same activity as SEQ ID NO:3.

This argument has been fully considered, but is not found persuasive. The Examiner agrees that Examples 6-8 of the specification prove that SEQ ID NO:3 has activity in promoting successful regeneration and functional reconnection of damaged neural pathways. However, amended claim 19 is drawn to:

> "A method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising administering a therapeutically or prophylactically effective amount of least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO:1, comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation codon of the open reading frame of the gene encoding TGF-R_{II} or a region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure"

As noted above, SEQ ID NO:3 is complementary to nucleotides 86729-86744 of SEQ ID NO:1, where SEQ ID NO:1 is the ORF of the gene encoding TGF-R_{II}. It is does not appear that SEQ ID NO:3 is directed to an oligonucleotide that is directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} or an oligonucleotide that is directed to the region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure as claimed in claim 19. Therefore, this argument has not been found to be persuasive.

Applicants third and final argument contends that Ogorelkova et al. present that antisense RNA or shRNA molecules with different but similar sequences show similar results for silencing TGF-R_{II} gene. Applicants contend that the teachings of Ogorelkova et al. support Applicant's opinion that oligonucleotides according to claim 19 show the same activity as SEQ ID NO:3, because they contain SEQ ID NO:3 or a sequence very similar to SEQ ID NO:3.

This argument has been fully considered, but is not found persuasive because as noted above, it does not appear that amended claim 19 is directed to SEQ ID NO:3 or even sequences that are similar to SEQ ID NO:3. For example, SEQ ID NO:3 is complementary to nucleotides 86729-86744 of SEQ ID NO:1, where SEQ ID NO:1 is the ORF of the gene encoding TGF-R_{II}. Because SEQ ID NO:3 is complementary to nucleotides 86729-86744 of the ORF of the gene encoding TGF-R_{II}, the Examiner cannot possibly see how SEQ ID NO:3 is synonymous to an oligonucleotide that is directed to the region encompassing the translation initiation codon of the ORF of the

gene encoding TGF-R_{II} as recited in amended claim 19. Further, because SEQ ID NO:3 is complementary to nucleotides 86729-86744 of the ORF of the gene encoding TGF-R_{II}, the Examiner cannot possibly see how SEQ ID NO:3 is synonymous to an oligonucleotide that is directed to the region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure as now recited in claim 19.

In summary, Ogorelkova et al. (Oligonucleotides, 2006 Vol. 16:2-14) teach that regarding the use of antisense RNA and short hairpin RNA for silencing TGF-βRII expression, antisense RNA were ineffective in silencing endogenous TGF-βRII. Ogorelkova et al. also teach:

> "The enduring challenge is to identify molecules that specifically and optimally silence a given target gene"; and
>
> "The fact remains that not all antisense RNAs designed against a particular target have an antisense effect, and selection of efficient antisense RNAs is largely a matter of trial and error"

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination and analysis of those oligonucleotides that are directed to the region encompassing the translation initiation codon of the ORF of the gene encoding TGF-R_{II} and those oligonucleotides that are directed to the region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure that act to promote successful regeneration and functional reconnection of damaged neural pathways in a mammal. As supported

by Ogorelkova et al., such analysis is replete with trial and error experimentation. Such experimentation represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success. Given the art recognized unpredictability of using antisense oligonucleotides directed to TGF-R_{II}, this determination would not be routine and would require undue trial and error experimentation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Sajjadi, Fereydoun G. can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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> For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Terra Cotta Gibbs/
March 4, 2010

/Sean R McGarry/
Primary Examiner, Art Unit 1635